Synthesis and Properties of Some Nitroxide α-Carboxylate Salts

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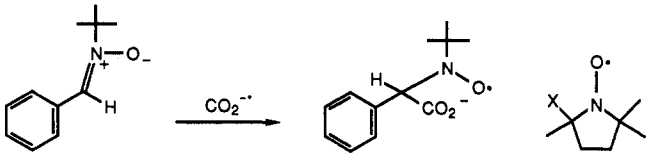
Nitroxide α-carboxylates **10** and **22a–e** were synthesized for evaluation as potential contrast-enhancing agents for magnetic resonance imaging applications. While pyrrolidine nitroxide carboxylate **10** was stable indefinitely, the free acid form **11** could not be isolated. Cyano amine **15** was obtained after workup by the $AlCl_3$-catalyzed addition of TMSCN to imine **13**. While **15** could be hydrolyzed to amide **17**, neither compound was a satisfactory precursor to nitroxide carboxylic acid **18**. Nitroxides **22a–d**, stable indefinitely when stored as the lithium salts, were conveniently prepared by reaction of the respective dianions of **20a–d** with 2-methyl-2-nitrosopropane followed by air oxidation. Reaction of **22d** with MeI gave **22e**. Structures in this series were confirmed through isolation of *N*-hydroxy intermediate **23** in pure form.

Owing to their paramagnetic nature, nitroxides have potential as contrast enhancing agents for magnetic resonance imaging (MRI) applications.[1] One limitation has been the tendency of nitroxides to undergo in vivo bioreduction to the diamagnetic *N*-hydroxy derivative.[2-4] Recently, Connor et al.[5] and others[6,7] have reported the detection of a persistent nitroxide, presumably nitroxide **2**, in spin-trapping[8] experiments such as the trapping of $CO_2^{\bullet-}$ by phenyl *tert*-butylnitrone (PBN) (**1**) in rat liver.

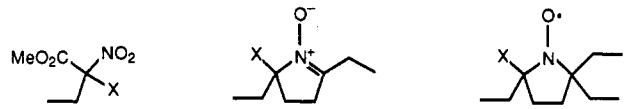


1 **2** **3** X = CO_2H; **4** X = CO_2^-

Preliminary results in one of our laboratories indicated that the nitroxide resulting from the spin trapping of $CO_2^{\bullet-}$ by PBN was not rapidly reduced by rat liver homogenate.[9] These results suggested that α-carboxylate nitroxides such as **2** might have application as MRI contrast enhancing agents if they can be obtained on a preparative scale. Earlier,[10] we had generated nitroxide carboxylic acid **3** and observed that this substance was not stable in the free acid form whereas its methyl ester was stable. At physiological pH, however, nitroxide **3** would be expected to exist as carboxylate ion **4**. Since the stability of this species under physiological conditions was not determined, it is possible that pyrrolidine nitroxide α-carboxylates[11] such as **4** also have potential for MRI. Collectively, these observations prompted us to undertake the preparative-scale synthesis herein reported of the representative α-carboxylate nitroxides **10** and **22a–e**.

Results and Discussion

Our first objective was to synthesize the pyrrolidine nitroxide α-carboxylate **10**. Michael addition of nitro ester **5**[12] to ethyl vinyl ketone gave nitro ketone **6** (44%), which underwent reductive cyclization upon treatment with zinc dust in aqueous ammonium chloride to give nitrone **7** (60%). Treatment of **7** with ethylmagnesium bromide



5 X = H; **6** X = CH_2CH_2CEt (=O); **7** X = CO_2Me; **8** X = C(OH)Et; **9** X = CO_2Me; **10** X = $CO_2^-Na^+$; **11** X = CO_2H

followed by $Cu(OAc)_2 \cdot H_2O$-catalyzed air oxidation of the crude mixture gave nitroxide methyl ester **9** (8%) after flash chromatography as a yellow oil. Crystalline nitrone alcohol **8** (16%) was also obtained and resulted from addition of the Grignard reagent to the ester carbonyl group of **7**. Nitroxide ester **9** was stable indefinitely when stored under N_2 at −20 °C.

Ester **9** was hydrolyzed with excess aqueous NaOH, giving an aqueous solution of nitroxide α-carboxylate **10**. Attempts to prepare nitroxide α-carboxylic acid **11** by acidification to pH 2 at 0 °C led to loss of the ESR signal and formation of a complex mixture of unidentified products. While the free acid **11** was not stable, the ESR

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(2) Griffeth, L. K.; Rosen, G. M.; Rauckman, E. J.; Drayer, B. P. *Invest. Radiol.* **1984**, *19*, 553.
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(7) Rehorek, D.; Benedix, M.; Thomas, P. *Inorg. Chim. Acta* **1977**, *25*, L100.
(8) Perkins, M. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 1.
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(10) Keana, J. F. W.; Heo, G. S.; Gaughan, G. T. *J. Org. Chem.* **1985**, *50*, 2346.
(11) Lin, J. S.; Tom, T. C.; Olcott, H. S. (*J. Agric. Food Chem.* **1974**, *22*, 526) reported the synthesis of L-proline nitroxide b, a nitroxide having three hydrogens on the α carbon, by oxidation of *N*-hydroxyproline a with *tert*-butyl hydroperoxide in ethanol. Nitroxide b was described as a light yellow-crystalline solid that was stable indefinitely in the solid state and had a half-life of about 16 h in pH 7 phosphate buffer at 24 °C. We were unable to obtain nitroxide b from a using the conditions of Lin et al. or a variety of other oxidizing conditions.

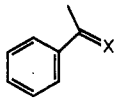
a b

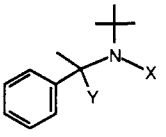
(12) Finkbeiner, H. L.; Wagner, G. W. *J. Org. Chem.* **1963**, *28*, 215.

0022-3263/89/1954-2417$01.50/0

signal intensity of a solution (pH 8) of salt **10** remained unchanged for at least 48 h. Evaporation of the solvent gave the crude solid salt, which was stable indefinitely. Preliminary studies[9] indicated that **10** was reduced rapidly by rat liver homogenate. Therefore, attention was turned toward the synthesis of other nitroxide α-carboxylates more closely patterned after nitroxide **2**.

The sterically hindered ketimine **13** was prepared according to the procedure of Weingarten et al.[13] by reacting *tert*-butylamine with acetophenone (**12**) in the presence of $TiCl_4$ in toluene. Trimethylsilyl cyanide reacted smoothly with **13** in the presence of a catalytic amount of $AlCl_3$[14] in benzene at 25 °C to give, via adduct **14**, crystalline nitrile **15** (75%) after workup. Several attempts





12 X = O

13 X = $NCMe_3$

14 X = $SiMe_3$; Y = CN

15 X = H; Y = CN

16 X = H; Y = CO_2H

17 X = H; Y = $CONH_2$

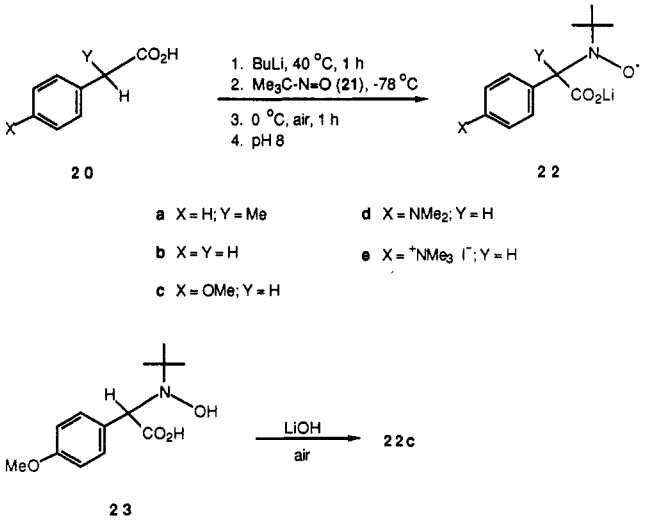
18 X = O•; Y = CO_2H

19 X = O•; Y = CN

to hydrolyze **15** to amino acid **16** were unsuccessful. For example, when **15** was treated with acetic acid–HCl[14] at 80 °C for 14 h, starting **15**, acetophenone (**12**), and some unidentified products were isolated. The formation of **12** could be explained through the elimination of HCN from **15** followed by hydrolysis of the resulting ketimine **13**. Attempted hydrolysis of **15** using sodium hydroxide[15] led to no useful products. Partial hydrolysis to amino amide **17** (36%) was achieved with concentrated H_2SO_4 for 2 days at 25 °C. Reasoning that oxidation of **15** to nitroxide **19** might then permit basic hydrolysis of the cyano group as a route to nitroxide α-carboxylic acid **18**, **15** was treated with MCPBA.[16] However, the resulting nitroxide, probably **19**, proved to be too unstable for further work.

At this point we opted for an approach that promised to give the nitroxide α-carboxylate directly. Dianions of carboxylic acids are known to under α-alkylation[17] and α-acylation[18] reactions. We reasoned that an analogous reaction[19] may take place with 2-nitroso-2-methylpropane (**21**).[20] Thus, the dianion of aryl acetic acid derivatives **20a–d**[21] were separately generated and then allowed to react with **21** at −78 °C (Scheme I). The reaction mixtures were then stirred open to air in order to oxidize the intermediate *N*-hydroxy lithio salt. After careful neutralization of the reaction mixture to pH 8, nitroxide α-carboxylates **22a–d** were obtained as impure yellow solids that resisted further purification by crystallization or precipitation techniques. Treatment of **22d** with excess MeI gave

Scheme I



the quaternary ammonium nitroxide **22e** as a hygroscopic yellow solid. Lithium carboxylate nitroxides **22a–e** appeared to be stable for months when stored at −20 °C.

It was estimated from the ESR signal intensity that nitroxides **22a–e** constituted 60–70% of their respective product mixtures. The ESR spectrum of **22b** in 0.1 M phosphate buffer pH 7.4 consisted of a characteristic triplet of doublets[5] with a_N = 16.0 G and a_H = 4.9 G. This spectrum remained unchanged for at least 48 h. In 0.1 M hydrogen phthalate buffer at pH 4, 90–95% of the ESR signal of these nitroxides disappeared after 5–10 min. In 1 M aqueous NaOH solution, a 50–60% decrease in ESR signal intensity of these nitroxides was observed after 3–4 h. Given that each contains an α-hydrogen atom, it is somewhat surprising that arylacetic acid derived nitroxide carboxylates **22b–e** with an α-hydrogen atom are so stable.[22] Apparently the presence of a benzene ring and an α-carboxylate group in close proximity to the nitroxyl moiety offer sufficient steric and electronic hindrance to prevent the disproportionation reaction.[22]

Confirmation of the assigned structures in this series of nitroxides was obtained from the reaction of the dianion derived from *p*-methoxyphenylacetic acid (**20c**) with **21** under our standard reaction conditions. In one set of experiments after the addition of **21**, the reaction mixture was immediately neutralized by careful addition of 10% aqueous HCl. Thus, hydroxylamine **23** was obtained in analytically pure form in 50% yield as a white solid. Air oxidation of a dilute solution of **23** in 10% aqueous LiOH solution gave a solution of nitroxide **22c**, the ESR spectrum of which was identical with that of **22c** obtained as described above.

Bioreduction studies with nitroxide carboxylates **22a–e** have been reported elsewhere.[23]

Experimental Section

Melting points were determined on a Thomas-Hoover oil bath apparatus and are uncorrected. Fully proton decoupled ^{13}C NMR spectra and ^1H NMR spectra were obtained with a General Electric QE-300 FT NMR spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in δ units. For ^{13}C NMR the chemical shift of $CDCl_3$ at 77.0 ppm was used as an internal standard. For ^1H NMR the residual protons in the deuterated

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(18) Krapcho, A. P.; Jahngen, E. G. E.; Kashdan, D. S. *Tetrahedron Lett.* **1974**, 2721.
(19) The reaction of 2-methyl-2-nitrosopropane with organometallic reagents leads to *N*-hydroxy amines that are readily oxidized to nitroxides. For example, see: Keana, J. F. W.; Prabhu, V. S.; Ohmiya, S.; Klopfenstein, C. E. *J. Org. Chem.* **1986**, *51*, 3456 and references cited therein.
(20) Calder, A.; Forrester, A. R.; Hepburn, S. P. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 803.
(21) For a convenient preparation of the ethyl ester of **20d**, see: Romanelli, M. G.; Becker, E. I. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 552.
(22) For a review on stable nitroxide free radicals, see: Keana, J. F. W. *Spin Labeling in Pharmacology*; Holtzman, J. L., Ed.; Academic Press: New York, 1984; Chapter 1.
(23) Keana, J. F. W.; Pou, S.; Rosen, G. M. *Magn. Reson. Med.* **1987**, *5*, 525.

solvent were used as internal standards: $CDCl_3$, 7.27 ppm; CD_3OD, 3.30 ppm. J values are in hertz. IR spectra were recorded either on a Beckman IR-10, a Sargent Welch 3-200, or a 5DXB FT-IR infrared spectrometer. X-Band ESR spectra were obtained in 0.1 M phosphate buffer pH 7.4 unless otherwise stated with either a Varian Model E-9 or a E-109 spectrometer. Silica gel column chromatography utilized Baker (60–200 mesh) silica gel. Flash chromatography utilized Grade 633, 200–425 mesh 60 A silica gel (Aldrich Co). Analytical TLC utilized Merck 60F-254 250 μm precoated silica gel plates. Preparative TLC utilized Analtech 1000 μm silica gel plates (20 × 20 cm). Spots were visualized either under ultraviolet light or by I_2 vapor. Elemental analysis were obtained from Desert Analytics Organic Microanalysis, Tuscon, AZ. All reactions were routinely run under a N_2 atmosphere. Solvents were routinely distilled. $MgSO_4$ was used as drying agent for organic solutions.

Methyl 2-Ethyl-2-nitro-5-oxoheptanoate (6). To a stirred solution prepared by adding sodium (0.64 g, 28 mmol) to dry methanol (160 mL) at 25 °C was added nitro ester **5**[12] (14.7 g, 0.100 mol). Then a solution of ethyl vinyl ketone (10.1 g, 0.12 mol, Aldrich) in dry methanol (40 mL) was added dropwise. After a 3-h reflux period, the resulting yellow solution was cooled to 0 °C and glacial acetic acid (10 mL) was added. The solvent was evaporated to afford an orange oil, which was distilled (110–116 °C/0.25 mmHg) to yield 15.7 g of crude yellow oil. This was redistilled (103–108 °C/0.25 mmHg) to yield 10.1 g (44%) of pure (NMR) **6** as a yellow oil: ^1H NMR δ 0.87 (t, 3, J = 7), 1.01 (t, 3, J = 7), 2.00–2.50 (m, 8), 3.76 (s, 3); IR ($CHCl_3$) 1755, 1720, 1555 cm^{-1}.

Methyl 2,5-Diethyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate 1-Oxide (7). Nitro ketone **6** (10.0 g, 43.7 mmol), 3:2 water–methanol (100 mL), and a solution of ammonium chloride (2.5 g) in water (10 mL) were combined in a 300-mL three-necked flask fitted with an overhead stirrer. Zinc dust (15.0 g) was added in small portions over a period of 30 min. After being stirred at 25 °C for 2 h, the mixture was filtered, and the filter cake was washed with methanol (5 × 50 mL). The combined filtrate was concentrated to 20 mL. The green solution was saturated with borax and then extracted with CH_2Cl_2 (5 × 50 mL). The combined CH_2Cl_2 extract was dried and evaporated to give 8.32 g of yellow green oil, which was distilled (114–116 °C/0.04 mmHg) to yield 5.20 g (60%) of **7** as a yellow oil, which was sufficiently pure (NMR) for the next experiment: ^1H NMR δ 1.00 (t, 3, J = 7), 1.24 (t, 3, J = 7), 2.00–3.00 (m, 8), 3.80 (s, 3); ^{13}C NMR δ 6.94, 9.10, 19.97, 25.54, 25.60, 28.41, 52.77, 82.26, 150.24, 170.99; IR (neat) 1740, 1600 cm^{-1}.

2-(Methoxycarbonyl)-2,5,5-triethyl-1-pyrrolidinyloxy (9) and α,α,2,5-Tetraethyl-3,4-dihydro-2*H*-pyrrole-2-methanol 1-Oxide (8). To a mechanically stirred solution of nitrone **7** (4.83 g, 24.3 mmol) in dry ether (100 mL) was added 35 mL of a 1 M ether solution of ethylmagnesium bromide at a rate sufficient to maintain gentle reflux. During the addition, a thick precipitate formed. To facilitate stirring, an additional 50 mL of dry ether was added. After 15 min at 25 °C, the mixture was refluxed for 1 h. The mixture was then poured into cooled saturated aqueous ammonium chloride (60 mL) and extracted with ether (6 × 50 mL). The extract was washed with brine, dried, and evaporated to give 3.10 g of a yellow oil, which was dissolved in methanol (25 mL) and stirred with $Cu(OAc)_2 \cdot H_2O$ (140 mg) for 1 h. The greenish mixture was evaporated, and the oily residue was purified by flash chromatography over silica gel (60 g) and eluted with 1:4 ether–hexanes. The middle of a fast-moving yellow band was collected, giving 459 mg (8%) of nitroxide **9** as a yellow oil: ESR ($CHCl_3$) a_N = 13.7 G; IR (CCl_4) 1730 cm^{-1}. Preparative TLC (1:1 ether–hexanes, R_f = 0.6) gave the analytical sample as yellow oil. Anal. Calcd for $C_{12}H_{22}NO_3$: C, 63.13; H, 9.71; N, 6.13. Found: C, 63.14; H, 10.00; N, 6.39.

The eluent was then changed to 4:1 ether–hexanes. A second yellow fraction was collected, giving 996 mg of the nitrone alcohol **8** as yellow solid. Crystallization from pentane at −20 °C yielded 879 mg (16%) of white crystalline **8**: ^1H NMR δ 0.82 (t, 3, J = 7), 0.89 (t, 3, J = 7), 0.96 (t, 3, J = 7), 1.14 (t, 3, J = 7), 1.25–1.27 (m, 12); IR ($CDCl_3$) 3200, 1615 cm^{-1}. Two recrystallizations from pentane at −20 °C gave the analytical sample of **8** as white small needles, mp 53–54 °C. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.74; H, 11.36; N, 6.37.

Hydrolysis of 9. To a stirred solution of nitroxide **9** (22 mg, 0.96 mmol) in THF (0.4 mL) was added 0.1 N NaOH (2 mL). The solution was stirred at 25 °C and monitored by TLC. After 3 h **9** had disappeared and the ESR spectrum of a 1-μL aliquot added to 100 μL of water showed a strong 3-line signal (a_N = 15.0 G). The solution was acidified at 0 °C with 10% aqueous HCl to pH 2 and extracted with ether. Neither the extract nor the aqueous layer showed any ESR signal. The ether solution was dried, and solvent was evaporated to yield 18 mg of a yellow oil. TLC (ether) showed several spots. The ^1H NMR spectrum indicated the presence of a complex mixture of unidentified products.

1,1-Dimethyl-*N*-(1-phenylethylidene)ethanamine (13). A modification of the procedure of Weingarten et al.[13] was employed. A Parr stainless steel pressure reactor was charged with distilled acetophenone (10.0 g, 83.0 mmol) and distilled *tert*-butylamine (24.0 g, 0.330 mol). A solution of $TiCl_4$ (12.0 g, 62.0 mmol) in dry toluene (40 mL) was added dropwise at 0 °C. The vessel was heated at 120 °C for 24 h, cooled to 25 °C, and unsealed, and the black reaction mixture was filtered and washed with ether (200 mL). The filtrate and ether washes were combined and evaporated, giving a dark red oil, which was distilled (65–75 °C/0.25 mmHg) in a Kugelrohr apparatus to yield 3.73 g (39%) of **13** as colorless oil: ^1H NMR δ 1.40 (s, 9), 2.35 (s, 3), 7.33–7.35 (m, 3), 7.71–7.75 (m, 2); IR ($CHCl_3$) 1682 cm^{-1}. This compound is known[24] but no physical data were reported.

α-[(1,1-Dimethylethyl)amino]-α-methylbenzeneacetonitrile (15). A modification of the procedure of Ojima et al.[14] was employed. A mixture of ketimine **13** (1.60 g, 9.14 mmol), distilled trimethylsilyl cyanide (2.50 mL, 18.3 mmol), $AlCl_3$ (70 mg), and dry benzene (10 mL) was stirred at 25 °C. After 12 h the reaction was complete (NMR). Concentration of the reaction mixture without removing the $AlCl_3$ caused reversal of the reaction to an extent of 40–50%. The following workup gave satisfactory results. After the reaction was completed, the suspension was diluted with ether (75 mL) and filtered through silica gel (10 g). The solvent was evaporated to yield 1.40 g (75%) of **15** as white crystals: ^1H NMR δ 1.11 (s, 9), 1.74 (s, 3), 7.30–7.39 (m, 3), 7.69–7.71 (m, 2); IR ($CHCl_3$) 3360, 2215, 1600 cm^{-1}. Recrystallization from hexanes gave the analytical sample of **15** as white needles, mp 50–52 °C. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.41; H, 9.09; N, 13.89.

Hydrolysis of 15 with AcOH–HCl. Via the procedure of Ojima et al.,[14] a solution of amine **15** (100 mg, 0.49 mmol) in 1:1 AcOH–HCl (1 mL) was heated at 80 °C for 8 h. A white precipitate and brown oil separated from the reaction mixture. Water (5 mL) was added, and the mixture was filtered. The filtrate was adjusted at 0 °C to pH 7 with 10% KOH and then extracted with $CHCl_3$. The extract was dried and evaporated to yield 68 mg of yellow oil, which was a 2:3 mixture of **13** and **15** (by NMR).

Oxidation of 15 with MCPBA. Via the procedure of Lai,[16] a stirred solution of amine **15** (100 mg, 0.49 mmol) in CH_2Cl_2 (15 mL) at −15 °C (dry ice and ethylene glycol bath) was treated with a solution of MCPBA (185 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) via a syringe pump over a period of 1 h. Over a 1-h period the solution became green, and a white precipitate of *m*-chlorobenzoic acid had formed. A 10-μL aliquot of the supernatent green solution was diluted with CH_2Cl_2 (1 mL) for analysis by ESR. The ESR spectrum exhibited a triplet (a_N = 15.0 G) which lost intensity during the scan. The original reaction mixture was filtered, and the filtrate was washed with aqueous 10% Na_2CO_3, dried, and evaporated to give 97 mg of sticky yellow solid, which was a mixture of several unidentified products (NMR and TLC). The material showed a weak ESR signal.

α-[(1,1-Dimethylethyl)amino]-α-methylbenzeneacetamide (17). A solution of amine **15** (500 mg, 2.47 mmol) in concentrated H_2SO_4 (5 mL) was stirred at 25 °C for 48 h and then poured into ice–water (25 mL). The solution was brought to pH 12 by addition of 50% aqueous NaOH. The mixture contained a white precipitate, which was filtered and washed with $CHCl_3$. The aqueous filtrate was extracted with $CHCl_3$. The combined $CHCl_3$ wash and extracts were dried and evaporated to give 480 mg of an oily solid. This was purified by flash chromatography over silica gel (10 g). Elution with 1:1 ether–hexanes gave 150 mg of starting

(24) Hubertus, A.; Ernst, O. D. *Synthesis* **1980**, 630.

amine 15. Elution with ether gave 195 mg (36%) of pure (NMR) 17 as a colorless viscous oil: ^{1}H NMR δ 1.14 (s, 9), 1.84 (s, 3), 6.07 (s, 1), 7.10 (s, 2), 7.21-7.34 (m, 3), 7.53-7.50 (m, 2); ^{13}C NMR δ 25.98, 32.78, 52.76, 65.41, 126.67, 127.84, 129.00, 146.63, 180.80; IR (CCl_4) 3480, 3425, 1685 cm^{-1}.

Carboxy(4-methoxyphenyl)methyl 1,1-Dimethylethyl Nitroxide Lithium Salt (22c). To a stirred solution of recrystallized 4-methoxyphenylacetic acid (**20c**, 166 mg, 1.00 mmol) in dry THF (2 mL) at -10 °C was added 0.85 mL (2.10 mmol) of 2.5 M *n*-BuLi in hexanes. The resulting yellow solution was stirred at 40 °C for 1 h [generation of the dianion (and also of the dianions derived from acids **20a,b**) was confirmed at this point by addition of a 50-μL aliquot of this solution to MeI (0.5 mL). After being stirred for 5 min at 25 °C, the solution was diluted with ether (5 mL) and then 10% HCl (0.5 mL) was added. The ether layer was separated, dried, and evaporated. An NMR ($CDCl_3$) spectrum of the residue indicated the clean formation of the corresponding α-methyl carboxylic acid in 90-95% yield], cooled to -78 °C, and then a solution of 2-methyl-2-nitrosopropane[20] (**21**, 130 mg, 1.5 mmol) in dry THF (2 mL) was added. The solution was allowed to warm to 25 °C over 3 h and then it was stirred for 30 min. The solution was cooled to 0 °C and allowed to stir open to air for 1 h. The resulting yellow-green solution was brought to pH 8 by addition of chilled 10% HCl. The organic solvent was evaporated, and the aqueous residue was diluted with H_2O (5 mL). The yellow aqueous solution was washed with ether (discarded), and then the aqueous phase was concentrated to dryness. The residue was dried under vacuum for 12 h. The resulting yellow solid was taken up in $CHCl_3$ (5 mL) and filtered. The filtrate was dried and evaporated to give 238 mg (95%) of crude **22c** as a yellow solid: ESR, an intense 6-line spectrum, a_N = 16.0 G, a_H = 4.9 G; IR ($CHCl_3$) 3373 (br), 1632 (sh), 1603 cm^{-1}.

α-Carboxy-α-phenylethyl 1,1-Dimethylethyl Nitroxide Lithium Salt (22a). The preparation was similar to that for **22c**. From 150 mg (1.00 mmol) of distilled 2-phenylpropionic acid (**20a**), 2.5 M *n*-BuLi in hexanes (0.84 mL, 2.10 mmol), and **21** (130 mg, 1.50 mmol) was obtained 201 mg (83%) of crude **22a** as a yellow solid: ESR, an intense 3-line spectrum, a_N = 17.0 G; IR ($CHCl_3$) 3380 (br), 1610 cm^{-1}.

Carboxyphenylmethyl 1,1-Dimethylethyl Nitroxide Lithium Salt (22b). The preparation was similar to that for **22c**. From recrystallized phenylacetic acid (**20b**, 136 mg, 1.00 mmol), 2.5 M *n*-BuLi in hexanes (0.84 mL, 2.10 mmol), and **21** (130 mg, 1.50 mmol) was obtained 194 mg (85%) of crude **22b** as a yellow solid: ESR, an intense 6-line spectrum, a_N = 16.0 G, a_H = 4.9 G; IR ($CHCl_3$) 3408 (br), 1626 cm^{-1}.

Carboxy[4-(dimethylamino)phenyl]methyl 1,1-Dimethylethyl Nitroxide Lithium Salt (22d). The preparation was similar to that for **22c**. From **20d**[21] (179 mg, 1.00 mmol), 2.5 M *n*-BuLi in hexanes (0.84 mL, 2.10 mmol), and **21** (130 mg, 1.50 mmol) was obtained 232 mg (95%) of **22d** as a crude yellow solid: ESR, an intense 6-line spectrum, a_N = 16.0 G, a_H = 5.0 G; IR ($CHCl_3$) 3367 (br), 1609 cm^{-1}.

Carboxy[4-(trimethylammonio)phenyl]methyl 1,1-Dimethylethyl Nitroxide, Iodide, Lithium Salt (22e). A solution of **22d** (100 mg, 0.41 mmol) in MeI (1 mL) was stirred for 24 h. The solvent was evaporated, and the residue was dried under vacuum for 12 h to yield 153 mg (97%) of crude **22e** as a hygroscopic yellow solid: ESR, an intense 6-line spectrum, a_N = 15.5 G, a_H = 4.0 G. It can be estimated from the ESR spectral intensity that about 60% of the mass of the yellow solid was **22e**.

***N*-[Carboxy(4-methoxyphenyl)methyl]-*N*-(1,1-dimethylethyl)hydroxylamine (23).** To a stirred solution of recrystallized *p*-methoxyphenylacetic acid (**20c**, 166 mg, 1.00 mmol) in dry THF (2 mL) at -10 °C was added 2.5 M *n*-BuLi in hexanes (0.85 mL, 2.10 mmol). The resulting yellow solution was stirred at 40 °C for 1 h and then it was cooled to -78 °C. A solution of **21** (130 mg, 1.5 mmol) in dry THF (2 mL) was added. The solution was allowed to warm to 25 °C over 3.5 h, and then the solution was quenched with chilled saturated NH_4Cl (10 mL). The mixture was filtered, the organic layer of the filtrate was separated, and the aqueous layer was extracted with ether. Chilled 10% HCl was added to the aqueous layer causing **23** to separate as a white precipitate (pH 5-6). This was collected and dried under vacuum for 24 h to yield 127 mg (50%) of analytically pure **23** as a white powder: mp 140-141 °C dec; ^{1}H NMR (CD_3OD) δ 1.40 (s, 9), 3.81 (s, 3), 4.89 (s, 1), 6.96-7.54 (AB q, 4, J = 8); IR (KBr) 3450, 3150, 1612 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.50; H, 7.63; N, 5.45.

Oxidation of 23. A solution of **23** (1.2 mg, 4.7×10^{-3} mmol) in 10% aqueous LiOH (1 mL) was stirred under air and monitored by ESR. After 10-15 min an ESR spectrum identical with that obtained above for **22c** was obtained. The intensity of the ESR signal reached a maximum after 60-70 min and began to diminish after about 180 min.

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Chiral Trifluoro Diamines as Convenient Reagents for Determining the Enantiomeric Purity of Aldehydes by Use of ^{19}F NMR Spectroscopy

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N,N'-Dimethyl-1,2-bis[*o*-, *m*-, and *p*-(trifluoromethyl)phenyl]-1,2-ethanediamines have been prepared. The meta trifluoro diamine was used as a chiral reagent for determining the enantiomeric purity of chiral aldehydes.

NMR spectroscopy is widely used for the determination of optical purity of chiral organic compounds.[1] Among the variety of proposed chiral derivatives,[2] one of the most common is α-methoxy-α-(trifluoromethyl)phenylacetic

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